Chapter

28 Antipsychotics (Tranquilizers)

1. INTRODUCTION

In general, **antipsychotics** (**tranquilizers**) are primarily employed for the treatment of symptoms in mental diseases, their overall influence being to free the mind from passion or disturbance and thus clam the mind *i.e.,* they cause sedation without inducing sleep.

Tranquilizers are drugs essentially used in the management and, treatment of psychoses and neuroses. They specifically exert their action on the lower brain areas to produce emotional calmness and relaxation without appreciable hypnosis sedation euphoria or motor impairment. In addition many of these drugs also display clinically beneficial actions, for instance skeletal muscle relaxants, antihypertensive, antiemetic and antiepileptic properties.

One school of thought even suggested that these drugs may be divided into *two* categories, namely : **major tranquilizers** (for **psychoses**) and **minor tranquilizers** (for **neuroses**) ; however, such an arbitrary categorization stands invalid because of their overlaping characteristic features.

More recently **antipsychotics** may be defined as—**'drugs' which ameliorate mental aberrations* that are invariably characteristic feature of the psychoses.**

Positive symptoms of psychoses essentially comprise of a host of disorders, such as : mild behavioural changes anxiety, delusions, hallucinations, and sclizzophrenias. Negative symptoms are usually designated by cognitive deficits, social withdrawl, apathy, and anhedonia.

Interestingly, '**psychoses**' may be organic which could be either trigger off or directly related to a variety of reasons, namely :

(*i*) particular toxic chemical influence *e.g.,* **delirium**—due to central anticholinergic drugs,

(*ii*) a N-methyl-D-aspartate (NMDA) antagonist *e.g.,* **phencylidine**.

(*iii*) a particular disease process *eg.,* **dementia** (cognitire deficit including memory impairment, and

(*iv*) idiopathic conditions *i.e.,* disease without clear pathiogenesis, as of spontaneous origin.

In a broader perspective the typical **'antipsychotics'** should ideally possess the following cardinal requirements, such as :

(*a*) high lipid solubility,

***Aberration :** Deviation from the normal.

(*b*) affinity for protein-binding (92–99%),

(*c*) large volume of distribution (v_d^{55}) *i.e.*, greater than 7 L.kg^{-1},

(*d*) variance in oral bioavailability (25–35%), and

(*e*) short plasma half-life between 10–20 hours.

It is, however, pertinent to mention here that though these drugs have a relatively shorter plasma half-life but their duration of action is much longer ; their metabolites may be found in the urine weeks even after the last terminal dosage ; and finally a good proportion of the drug are adequately sequestered in the various tissues.

2. CLASSIFICATION

Antipsychotics may be classified under the following categories, namely :

(*a*) Reserpine and Related Alkaloids

(*b*) Alkylene Diols

(*c*) Diphenylmethane Compounds

(*d*) Phenothiazine Compounds

(*e*) Dibenzazepines

(*f*) Butyrophenones

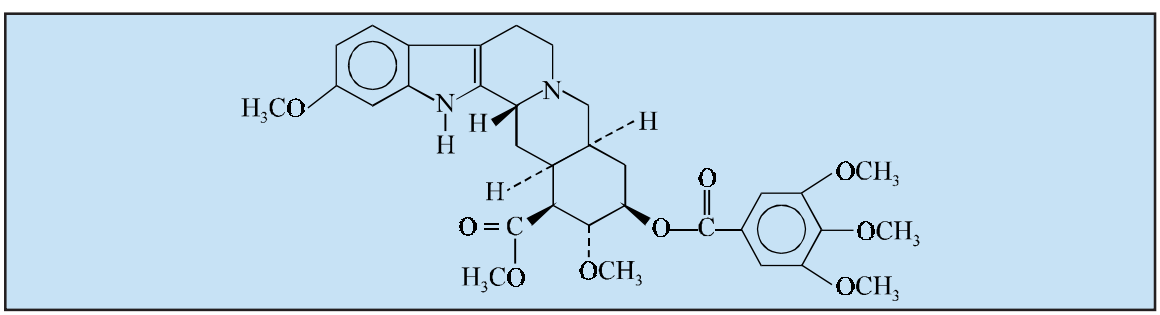
(*g*) Azaspirodecanediones

2.1. Reserpine and Related Alkaloids

The roots of *Rauwolfia serpentina*, a climbing shrub indigenous to India, and named after the German botanist **Rauwolf,** contains an alkaloid **Reserpine** which was reported to possess both tranquilizing and hypotensive properties.

Examples : Reserpine and **Deserpidine**.

A. *Reserpine* BAN, USAN, INN,



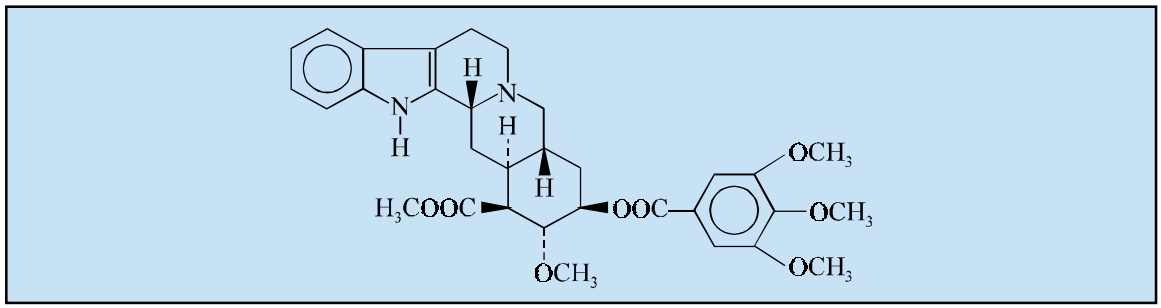
Methyl 18 β-hydroxy-11,17 a-dimethyoxy-3β, 20α-yohimban-16β-carboxylate 3,4,5-trimethoxybenzoate (ester) ; BP ; USP ; Int. P ;

Serpasil$^{(R)}$ (Ciba-Geigy) ; SK-Reserpine$^{(R)}$ (Smith Kline & French) ; Sandril$^{(R)}$ (Lilly) ;

It has central depressant and sedative actions and a primarily peripheral antihypertensive effect accompanied by bradycardia. It is also used for the management and treatment of hypertensive specifically in patients with mild labile hypertension associated with tachycardia.

Dose. *As sedative in anxiety states and chronic psychoses : 0.1 to 1 mg daily doses. For hypeprtension-in adults : 250 to 500 mcg daily for about 2 weeks ;*

B. *Deserpidine* INN, USAN ; *Desipraminum* BAN ;



II-Desmethoxyreserpine ; BP ; USP ;

Harmonyl(R) (Abbott) ; Pertofram(R) (Ciba-Geigy) ;

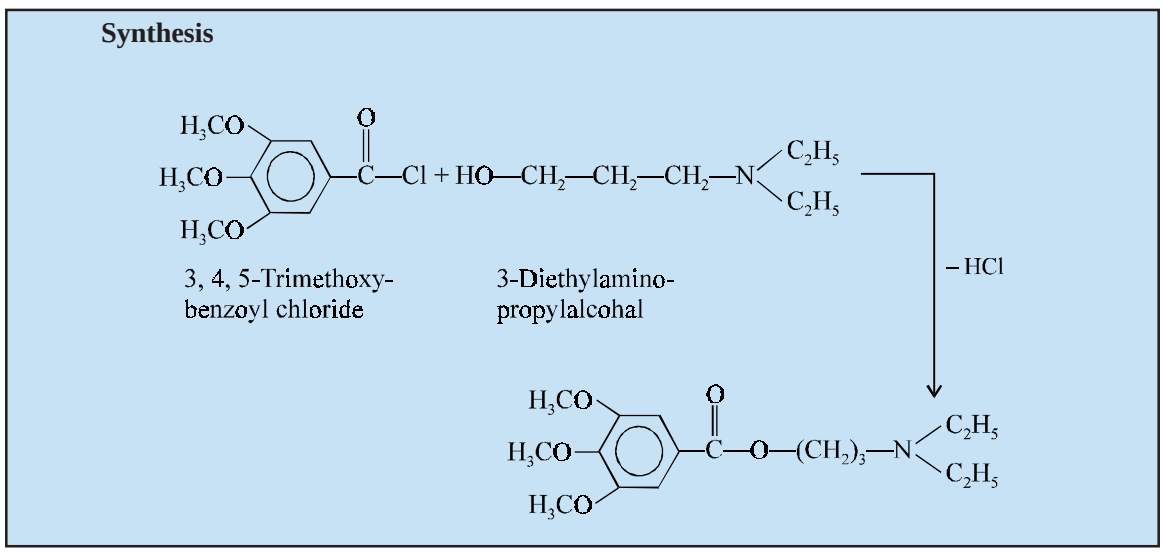
Its actions and uses are very much similar to those described under reserpine.

Dose. *For psychiatric treatment : Average, initial, 500 mcg daily with a range of 0.1 to 1 mg ; For antihypertension ; initial 0.75 to 1 mg daily subsequently reduced to a maintenace dose of about 250 mcg per day.*

Miller and Weinberg (1956) observed that even the simple tertiary amines having the trimethoxybenzoyl group exhibits the reserpine-like activity.

Example : 3-Diethylamino propyl ester of 3, 4, 5-trimethoxy benzoic acid.

Synthesis



It is prepared by the interaction of 3, 4, 5-trimethoxybenzoyl chloride with 3-diethylaminopropyl alcohol with the elimination of hydrochloric acid.

It is found to possess about 1/3rd the activity of **reserpine**.

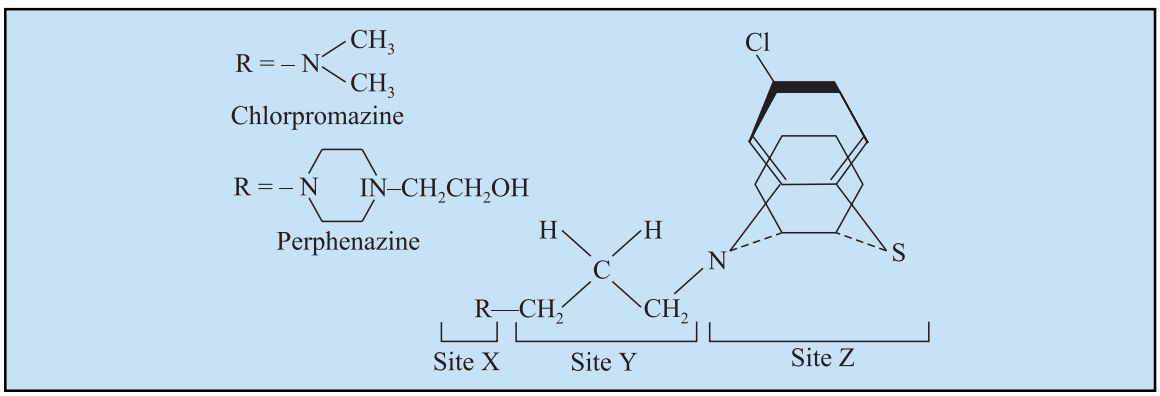
2.1.1. Mechanism of Reaction

The mechanism of reaction of the '**drug**' discussed under Section 2.1 shall be treated separately as under :

2.1.1.1. Reserpine

The '**drug**' exerts its action to cause significant inhibition of both **neuronal** and **chromaffin granule transporters**. Consequently, the **catecholamine accumulation** gets blocked appreciably. As a net overall effect the depletion is rather slower and less complete in the adrenal medulla in comparison to other tissues. Therefore, the strategic prevention of such storage ability/capacity, the '**drug**' at its initial primary state affords a distinct **catecholamine** release. Subsequently, a marked and pronounced '*depletion of transmitter*' commences that usually prolongs for days through weeks. The effects of reserpine seem to be irreversible absolutely.

Reserpine exerts its antihypertensive action by virtue of its adrenergic neutronal blockade consequent to depletion of the catecholamines-containing granudles of the postganglionic sympathetic neuron. It, however, depletes both brain **catecholamines** and **seritonins**.



Phenothiazines exert their antipsychotic potency by interacting with a receptor at three marked sites X, Y, Z to produce a singificant response. The order of specific structural requirement at these sites is YZX. However, a three-carbon chain at site Y affords an optimal antipsychotic activity.

The apparant variance in the efficacy of oral administration of **reserpine** is due to the fact that it gets absorbed very poorly as well as erratically from the ensuing GI tract. Importantly and characteristically the '*drug*' bears a relatively longer latency of onset, and followed by a prolonged duration of action.

Note. Combinations of resperpine, with a diuretic enhances the efficacy of the former significantly.

2.1.1.2. Deserpidine

It essentially possesses almost similar phermacological activity and mechanism of action of that of **'reserpine'** discussed under Section 2.1.1.1 above.

2.2. Alkylene Diols

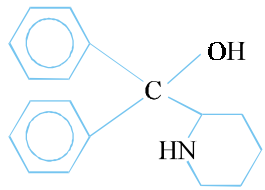
Alkylene diols are also referred to as **'propanediol carbamates'** have been used as tranquilizer. Two mportant members of this classification, namely : **meprobamate** and **tybamate** have been discussed in the Chapter-8 on **'Muscle Relaxants'** in this book.

2.3. Diphenylmethane Compounds

A number of **diphenylmethane** derivatives have been synthesized that exhibit antipsychotic activities.

A few such compounds are described below, namely : **Pipradrol** ; **Captodiame** ; **Hydroxyzine** ; **Benactyzine** ;

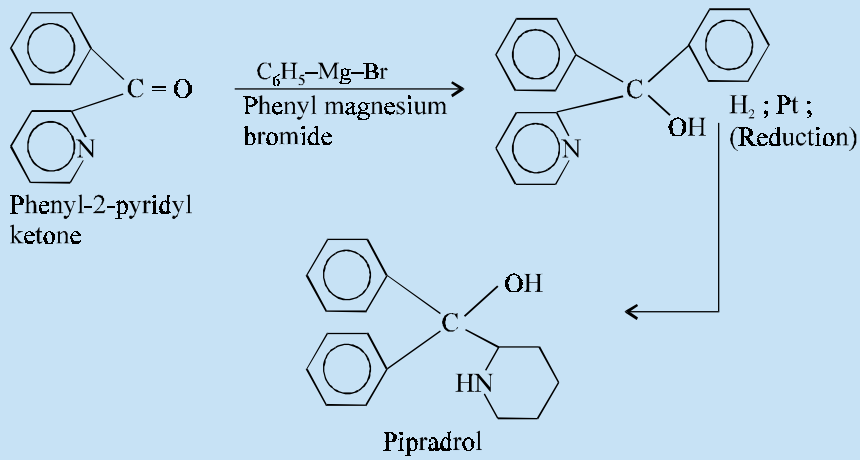
A. *Pipradrol* INN, BAN, *Pipradrol Hydrochloride* USAN,



α, α-Diphenyl-2-piperidine methanol ; Pipradrol Hydrochloride BP ;

Meratran(R) (Merrell Dow) ;

Synthesis

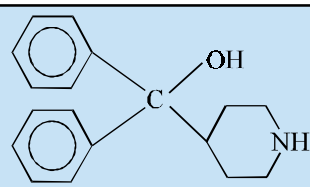


It is synthesized by **Grignard reaction** of phenyl-2-pyridyl ketone with phenyl magnesium bromide followed by catalytic reduction to get the official compound.

It is used for the treatment of functional fatigue and various types of depressions.

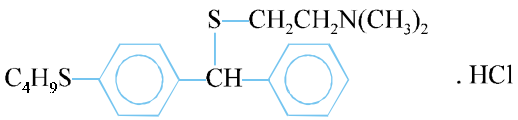
Dose. *Usual, 2.5 mg twice daily.*

The corresponding 4-piperidyl derivative pipradrol is also a **tranquilizer** used under the name of **Azacyclonal**.



The drug is prepared from phenyl ketone exactly in the same manner as that of **pipradrol**. It has the same application as that of its isomer.

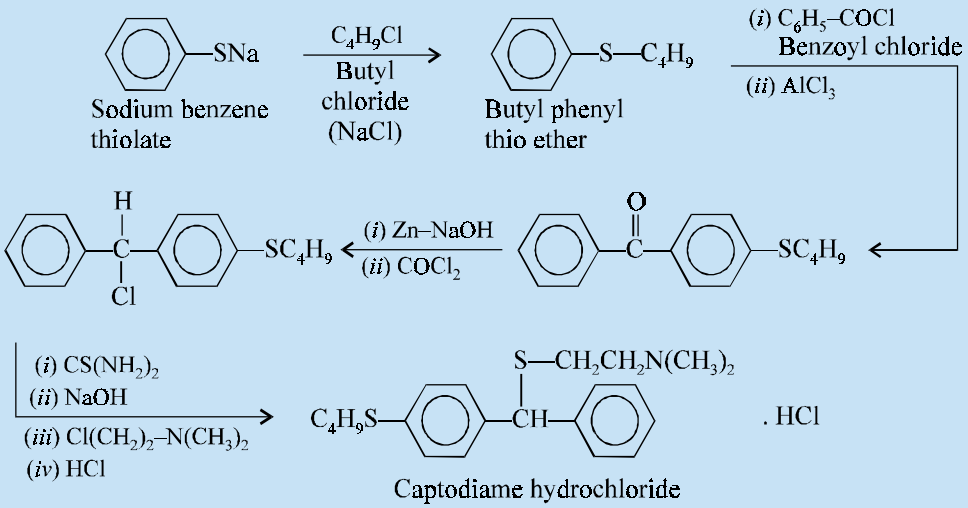
B. *Captodiame* INN, BAN ; *Captodiame Hydrochloride* USAN ;



2-[*p*-(Butylthio)-α-phenylbenzylthio]-N, N-dimethylethylamine hydrochloride ;

Covatin(R) (Warner-Lambert) ;

Synthesis

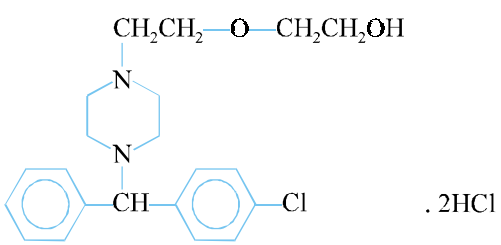


Butylphenyl thioether is first prepared by the interaction of sodium benzenethiolate and butyl chloride. The resulting product on treatment with benzoyl chloride and aluminum chloride yields butyl-p-benzoyl phenyl thioether. This on reaction with zinc and sodium hydroxide and carbonyl chloride yields an intermediate. The intermediate on treatment with thiourea, sodium hydroxide, 2-dimethyl amine ethyl chloride and hydrochloric acid gives rise to the desired compound.

It is used for the treatment of anxiety and tension. It is an excellent nonhypnotic sedative.

Dose. *For anxiety and tension : 50 mg three times per day.*

C. *Hydroxyzine* INN, BAN ; *Hydroxyzine Hydrochloride* USAN ;

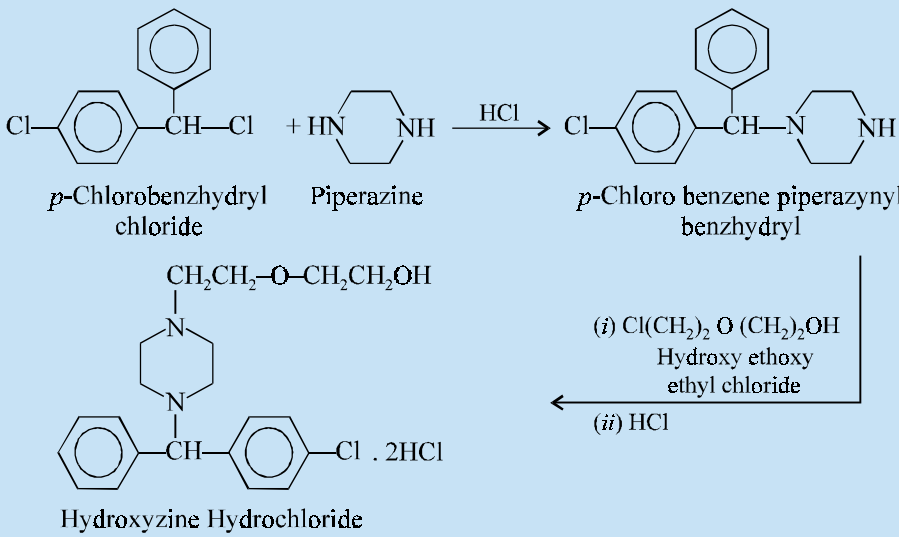


Ethanol, 2-[2-[4-chlorophenyl) phenyl methyl]-1-piperazinyl]ethoxy]-, dihydrochloride ;

Hydroxyzine Hydrochloride USP ;

Atarax(R) (Roerig) ; Orgatrax(R) (Organon) ;

Synthesis

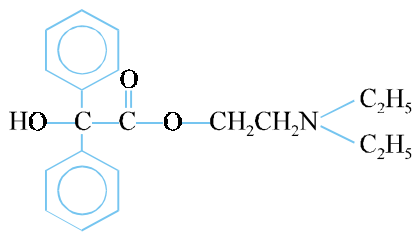


It is prepared by interacting p-chloro benzhydryl chloride with piperazine to obtain p-chlorobenzene piperazynyl benzhydryl which is subsequently treted with β-hydroxy ethoxy ethyl chloride to give the hydroxyzine base. They official compound may be finally obtained by treating with hydrochloric acid.

It is employed for pre-and postoperative sedation. It has also been used successfully in the treatment of anxiety, tension and agitation.

Dose. *Adult, IM injection as the hydrochloride in doses of 25 to 100 mg every 4 to 6 hrs ; Children : 1 mg per kg body weight im for pre-and postoperative sedation.*

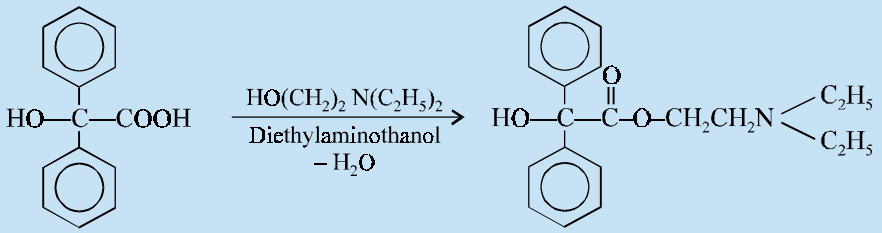
D. *Benactyzine* BAN ; USAN ; *Benctyzine Hydrochloride* INN ;



2-Diethylaminoethyl benzilate ; BPC (1959) ;

Suavitil(R) (Dumax) ; Nutinal(R) (Boots) ; Cevanol(R) (ICI) ; Parasan(R) (Medix) ;

Synthesis



Benzilic acid Benactyzine

It may be prepared by treating benzilic acid with diethylamne ethanol resulting the official compound with the elimination of a molecule of water.

2.3.1. Mechanism of Action

The mechanism of action of some of the medicinal compounds described under Section 2.3 shall now be dealt with individually in the sections that follows :

2.3.1.1. Pipradrol Hydrochloride

The '**drug**' exerts its action as a stimulant of the central nervous system. Perhaps this could be the reason it is invariably included in multingredient preparations of combat antipsychotic profile to a great extent.

2.3.1.2. Captodiame Hydrochloride

The '**drug**' exerts its therapentic action to combat various types of anxiety disorders *viz.*, generalized anxiety disorders, panic attacks, phobic disorders, obsessive-compulsive disorder, post-tranmatic stress disorder, and mixed anxiety and depressive disorders. Perhaps the **'drug'** acts as a atypical antisychotic agent by virtue of its reduced tendency to produce the extrapyramidal effects.

2.3.1.3. Hydroxyzine Hydrochloride

The '**drug**' exhibits antichloinergic action ; and, therefore, its overall effects may be additive with those of **atropine** and other **belladona alkaloids**. Likewise, a host of other therapeutically potent sedative drugs it essentially requires a stringent precautionary measure with regard to its dose adjustment in such subjects who are on other **CNS-depressant drugs**. In the same vein, when employed as a preanaesthetic medication with other agents *e.g.,* **barbiturate(s)**, **mepreidine**, the dosage regimen need to be adjusted on an individual basis cautiously.

Note. The potentiating effect of this drug should always be taken into consideration when it is employed in conjunction with CNS-depressants for instance : barbiturates and narcotics.

2.3.1.4. Benactyzine Hydrochloride

The **'drug'** is found to show its action as an antidepressant as well as antimuscarinic activity. However, the antidepressant therapy has mainly been accomplished either *via* the **monoamine oxidase (MAO)** inhibitors or *via* the **reversible inhibitors (RIMAs)**.

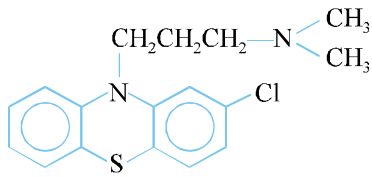
2.4. Phenothiazine Compounds

The discovery of **phenothiazine** as an anthelmintic dates back to 1883, however, its antithistaminic activity was revealed in 1937. The comintuous search for better drugs ultimately resulted into the synthesis of **chlorpromazine** in the famous **Rhone-Poulenc Laboratories in France** in the year 1950 which was

found to possess remarkable ameliorative effect on anxiety, agitation and psychoses. This ultimately led to the synthesis of a host of structural analogues of **chlorpromazine** that were found to be useful as antipsychotics.

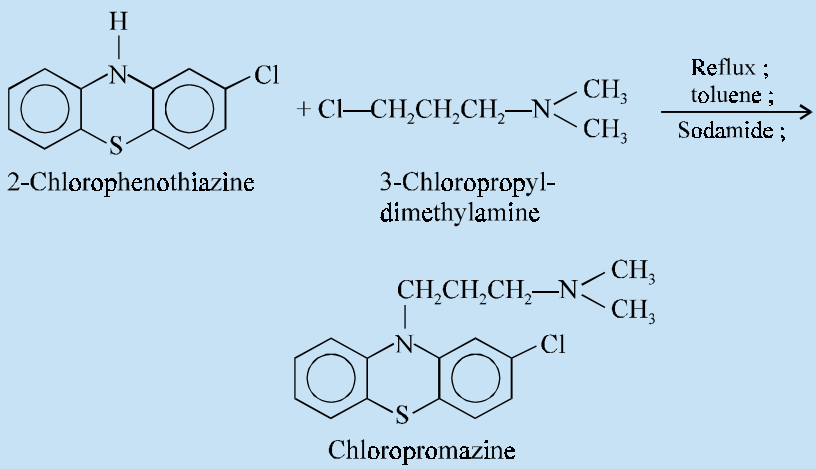
A few typical examples from this class of compounds are discussed here, namely ; **Chlorpromazine**, **Perphenazine**, **Thioridazine**.

A. *Chlorpromazine* INN, BAN, USAN,



2-Chloro-10-[3-(dimethylamino) propyl] phenothiazine ; BPC (1973) ; USP ; Thorazine(R) (Smith Kline French) ; Promapar(R) (Parke-Davis) ; Megaphen(R) (Bayer) ; Promacid(R) (Knoll) ;

Synthesis

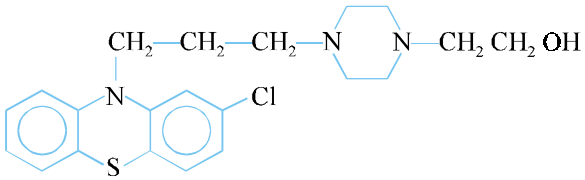


It is prepared by refluxing a toluene solution of 2-chlorophenothiazine and 3-chloropropyl dimethylamine in the presence of sodamide for several hours, followed by filtration and removal of toluene under reduced pressure.

It enjoys the reputation for being the **tranquilizer** of the **phenothiazine compounds**. It is found to be effective in the management of manifestations of psychotic disorders and manic depressive illness (*manic pahse*), apprehension and anxiety and prior to surgery. It is also used for the treatment of moderate to severe agitation.

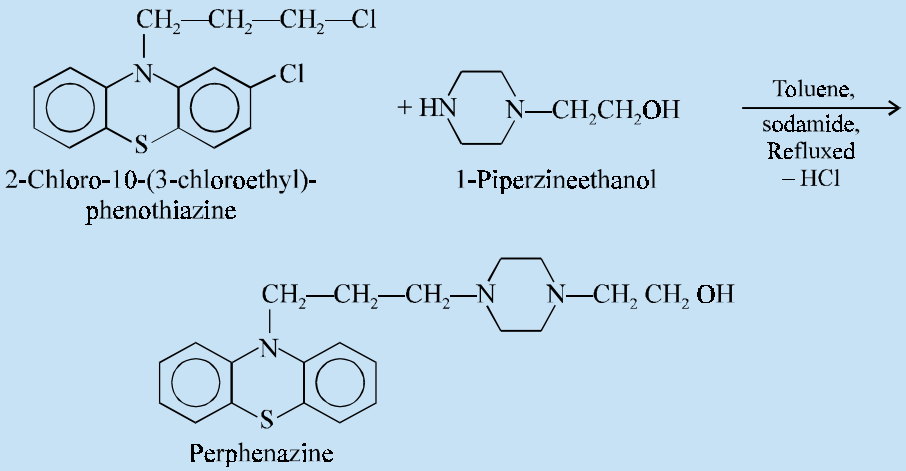
Dose. *Tranquilizer : Adults, oral, usual, 10 to 50 mg 2 or 3 times daily to a total dose of 1 g daily when indicated ; 1m, 25 to 50 mg repreated in 1 hour upto a total dose of 1 g per day ; Children, oral, 0.55 mg/kg every 4 to 6 hours ; im, 0.55 mg/kg every 6 to 9 hours.*

B. *Perphenazine* INN, BAN, USAN,



Piperazineethanol, 4-[3(2-chloro-10-phenothiazine-10 yl) propyl]- ; BP (1973) ; USP ; Trilafon$^{(R)}$ (Schering-Plough) ;

Synthesis

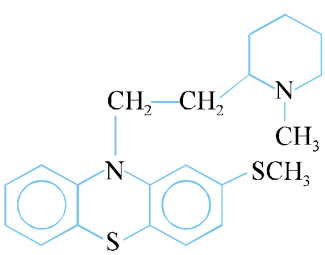


It is prepared by refluxing a toluene solution of 2-chloro-10-(3-chloro-propyl) phenothiazine with 1-piperazineethanol in the presence of sodamide.

It is used for the mangement and treatment of neuroses.

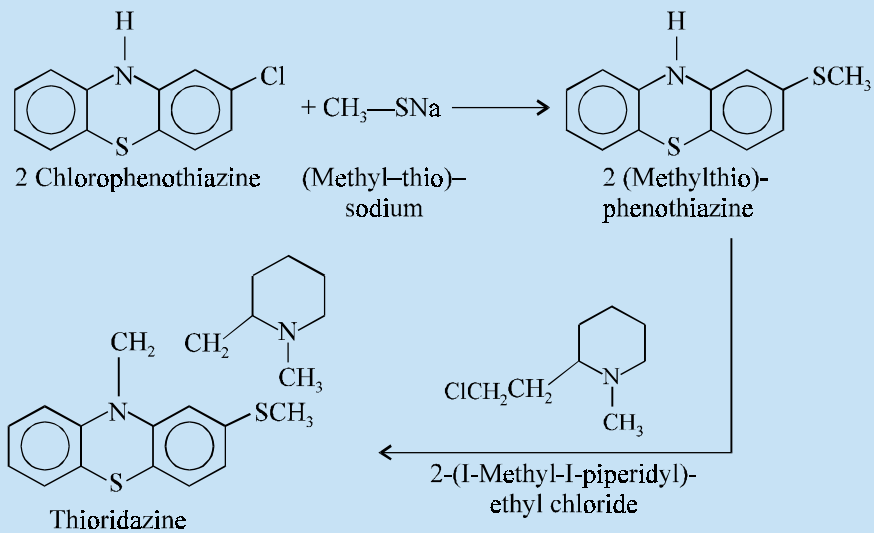
Dose. *Usual, oral, nonhospitalized patients, 2 to 8 mg thrice daily ; hospitalized patients, 8 to 16 mg 2 to 4 times a day ; im, 5 to 10 mg initially, followed by 5 mg in 6 hours.*

C. *Thioridazine* INN, BAN, USAN,



10[2-Methyl-2-piperidyl) ethyl]-2-(methylthio)-phenothiazine ; BP (1973) ; USP ;
Mellaril$^{(R)}$ (Sandoz) ;

Synthesis



It is prepared in two steps. First step being the preparation of 2-(methylthio) phenothiazine by the interaction of 2-chlorophenothiazine with (methyl-thio) sodium. The second step involves the condensation of the resulting product with 2-(1-methyl-1-piperidyl) ethyl chloride to obtain the official compound.

Its actions and uses are very much identical to those of **chlorpromazine** discussed earlier.

Dose. *Usual, initial, for psychoses : 50 to 100 mg 3 times daily ; for nonpsychotic emotional disturbances for instance tension and anxiety : 30 to 200 mg per day ; for children having behavioural disorders : 1 mg per kg body weight per day in divided doses.*

2.4.1. Mecha]nism of Action

The mechanism of action of drugs described under Section 2.4 shall now be dealt with as below :

2.4.1.1. Chlorpromazine Hydrochloride

The '**drug**' shows its effectiveness for the control and management of symptoms associated with mild alcohol withdrawl, moderate to acute agitation, and observed hyperactivity or apparent aggressiveness particularly in mentally disturbed children by exerting its action on the CNS.

The '**drug**' shows volume of distribution (v_d^{ss}) after a single oral administration to be 80.6 L kg^{-1}, whereas a reduction to 21.8 L kg^{-1} (upto 25%) *via* IM administration. Hence, the 4-fold difference actually reflects directly upon the low availability *via* the oral route (32%). Almost 100 metabolites of chlorpromazine (CPZ) in humans are known, of which only two are found to be **active** in humans, namely : (*i*) **11-hydroxy CPZ** ; and (*ii*) **17-hydroxy-CPZ**.

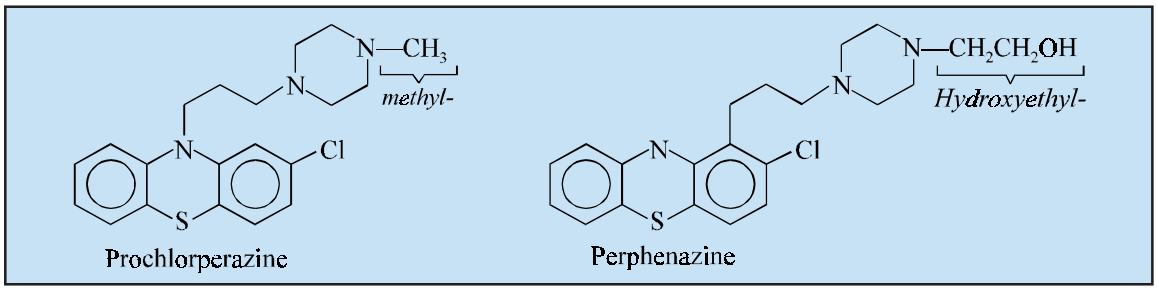
The effective plasma concentration of **CPZ** specifically in severe schizophrenic subjects have been demonstrated to vary from 30—300 ng. mL^{-1}, and plasma levels from 750-1000 ng. mL^{-1}.

CAUTION. Levarterenol and phenylephrine are employed invariably for the control and management of hypotension.

2.4.1.2. Perphenazine

The '**drug**' exerts its action very much similar to the one described under chlorpromazine (Section 2.4.1.1).

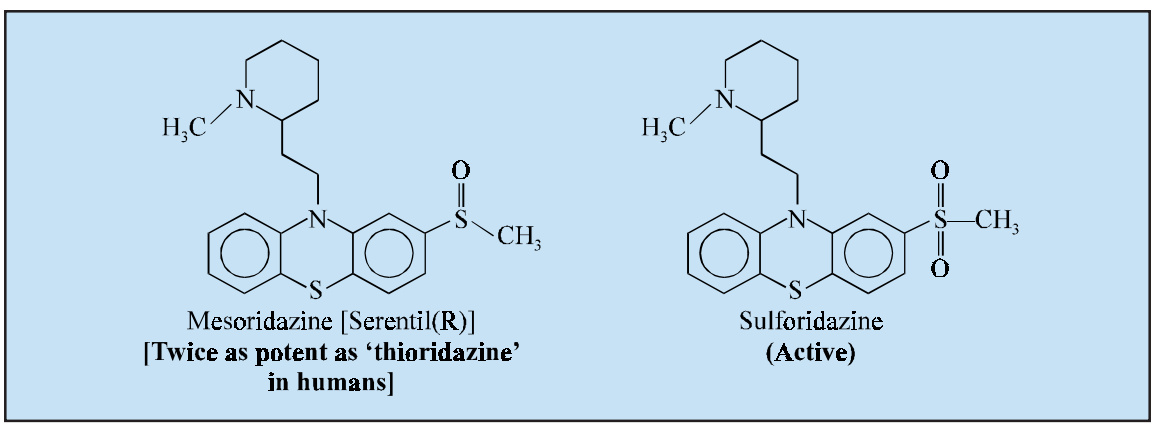
SAR of Perphenazine. It differs chemically from **prochlorperazine** only with respect to the substitution of a hydroxyethyl (—C_2H_5OH) moiety for the methyl moiety of the latter drug as shown below :



2.4.1.3. Thioridazine Hydrochloride

The '**drug**' exerts its bear minimum antimetic activity and thereby gives rise to minimal **extrapyramidal stimulation (EPS)**. Drowsiness and sedation are predominantly less intense in this '**drug**' in comparison to either **CPZ** and other similar drug substances.

The half-life seems to be particularly to a *multiphasic status i.e.*, having an *early phase* ranging between 26-36 hours ; and a definitive *late phase* varying between 26-36 hours. The '**drug**' gets bound to plasma protein to the extent of 96-99%. Importantly, **thioridazine** gets sulfoxidized *in vivo* into the metabolities **mesoridazine** plus a small quantum of **sulforidazine,** both of which are **active** pharmacologically.

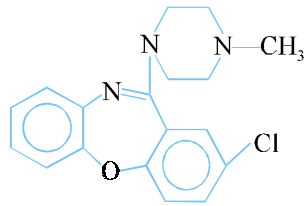


2.5. Dibenzazepines

Dibenzazepine analogous constitute another category of antisychotics which have gained recognition in late sixties.

A few important member of this class are described here, namely ; **Loxapine** ; **Clozapine** ;

A. *Loxapine* BAN, USAN, INN,



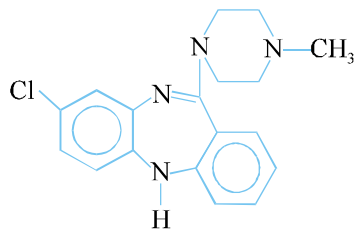
Dibenz [b, f][1, 4] oxazepine, 2-chloro-11-(4-methyl-1-piperazinyl)-;

Loxitane(R) (Lederle) ;

Its antipsychotic actions are similar to those of **chlopromazine**.

Dose. *Usual, oral, for psychoses : 20 to 50 mg per day initially, split in 2 to 4 divided doses.*

B. *Clozapine* INN, BAN, USAN,



5 H-Dibenzo [*b, e*][1, 4] diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-;

Clozaril(R) (Sandoz) ;

It is a **dibenzodiazepine derivative**. It is an unusual antipsychotic agent which hardly produces any extrapyramidal symptoms. It possesses the ability to suppress symptoms of tardive dyskinesia.

2.5.1. Mechansim of Action

The mechanism of action of **loxapine** and **clozapine** shall now be described as under :

2.5.1.1. Loxapine Succinate

The exact mechanism of action of this '**drug**' is not yet established. It has been observed that the absorption soonafter oral administration is almost complete. Furthermore, the '**drug**' after distribution to tissues invariably gets metabolized and subsequently excreted *via* urine and faeces, largely in the first 24 hours. By virtue of the fact that it may give rise to possible **anticholinergic activity,** it must be employed with great caution in such patients who have either a history of *glaucoma* or *urinary retention* problems.

2.5.1.2. Clozapine

The '**drug**' is found to very effective and relatively rapid-acting in the treatment of schizophrenia perhaps due to several of its CNS effects that essentially differ from a host of other members of antipsychotics. It is also believed beyond any reasonable doubt that the antipsychotic actions of this '**drug**' are basically of more complex nature in comparison to other antipsychotic drugs. In addition to the above observations the '**drug**' specifically blocks **dopamine** D-2 and 0-1 receptors essentially in the *mesolimbic** and *mesocortical brain regions*, which may also involve covertly and overtly **cholinergic**, **seretonergic** and **noradrenergic** systems.

---

* Medium sized border of a part.

Contrary to the usual activity of antipsychotics, **clozapine** exhibits *regional specific anti-dopaminergic profile* having, relatively mild antagonism on the extrapyramidal dopaminergic action ; and this could be responsible for its low prepensity to produce extrapyramidal side effects *e.g.*, dystonias, tardive dyskinesia.* It also causes greater blockade of dopamine D-1 receptors ; and however, it is not yet established whether such action precisely contributes to its antipsychotic therapeutic activity.

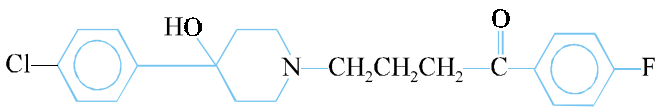
Clozapine gets absorbed rapidly from the GI tract and extensively metabolized during the first pass through the liver. The peak plasma levels usually take place in about 1.5 hour after a single oral dosage. It has been observed that there exists a **sixfold interindividual variability** in steady state plsma concenrations in subjects administered with high dosage regimen of this **'drug'**. The **'drug'** and its metabolites are excreted mostly in the urine.

2.6. Butyrophenones

Janssen and coworkers synthesized a number of **butyrophenones** having antipsychotic potency similar to **chlorpromazine** :

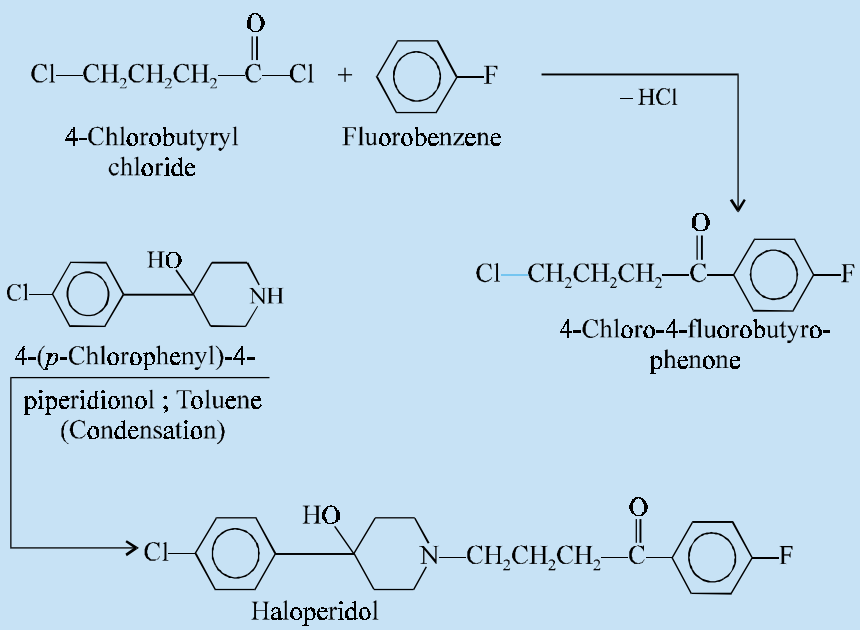
Examples : Haloperidol ; **Droperidol** ;

A. *Haloperidol* INN, BAN, USAN,



4-[4-(*p*-Chlorophenyl)-4-hudroxypiperidino]-4′-fluorobutyrophenone ; BP (1973) ; USP ; Haldol(R) (McNeil) ; Aloperidin(R) (Janssen) ; Serenace(R) (Searle) ;

Synthesis



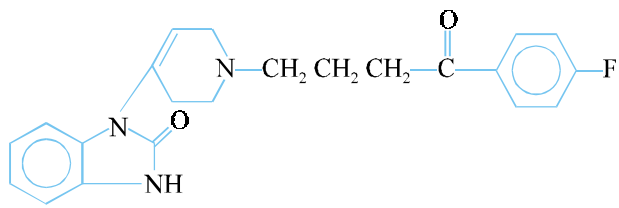
*A condition of slow, rhythmical, automatic sterotyped movements, either generalized or in single muscle groups. These occur as an undesired effect of therapy with **phenothiazine**s (psychotropic drugs).

4-Chloro-4′-fluorobutyrophenone is first prepared by the **Friedel-Craft's reaction** between 4-chlorobutyl chloride and fluorobenzene which is subsequently condensed with 4-(*p*-chloro-phenyl)-4-piperidinol in toluene to give the official compound.

It is useful in the treatment of anxiety, tension, moderate to severe agitation, hostility, and hyperactivity. It also finds its usefulness in schizophrenia, psychotic reactions related to organic brain syndromes and in *Gilles de la Tourette's disease* (unusual barking).

Dose. *Usual, adult, oral, 0.5 to 5 mg 2 or 3 times daily ; Intramuscular, 3 to 5 mg ;*

B. *Droperidol* INN, BAN, USAN,



1-[1-[3-(*p*-Fluorobenzoyl) propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone ; USP ;

Inapsine$^{(R)}$ (Janssen) ;

It is employed for the control of agitated patients in acute psychoses. It is normally used in conjunction with an analgesic for instance fantanyl citrate or phenoperidine hydrochloride to maintain the patient in a state of neuroleptanalgesia whereby he is calm and indifferent to his surroundings and able to cooperate with the surgeon.

Dose. *Premeditation : iv or im, 2.5 to 10 mg 30 to 60 minute before induction ; Induction : usual, IV, 2.5 mg per 20 to 25 lb. ; maintenance : usual, IV : 1.25 to 2.5 mg.*

2.6.1. Mechanism of Action

The mechanism of action of the medicinal compounds discussed under Section 2.6 shall now be treated individually in the sections that follows :

2.6.1.1. Haloperidol

The '**drug**' exhibits its activity by calming down excessive motor activity quite prevalent in '*hyperactive children*' having conduct disorders, such as : aggressivity, mood lability, impulsivity, poor frustration tolerance, and difficulty in sustaining attention.

Haloperidol shows bioavailability extending upto almost 60% *via* oral administration. Interestingly, its elimination half-life *via* oral route varies between 12-38 hours, which eventually gets lowered between 10-19 hours after IV administration. The usual therapeutic plasma concentrations ranges between 3-10 ng mL^{-1}.

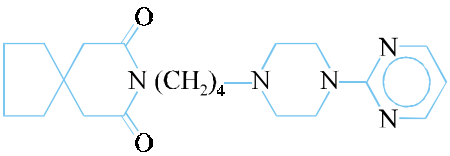
2.6.1.2. Droperidol

The '**drug**' exhibits relatively low therapeutic potency, medium extrapyradimal toxicity, high sedative effect, and above all high hypotensive action. However, it is most frequently employed in the form of its combination [**Innovar$^{(R)}$**] along with the narcotic agent **fentanyl** [**Sublimaze$^{(R)}$**] preanaesthetically.

2.7. Azaspirodecanediones

Azaspirodecanediones have gained prominence as antipsychotic agents recently. In mid-eighties a member of this family, namely, **buspirone** was introduced in the United States and is discussed here.

A. *Buspirone* INN, BAN ; *Buspirone Hydrochloride* USAN,



8-Azaspiro [4, 5] decane-7, 9-dione, 8-4-[4-(pyramidinyl)-1-piperazinyl]butyl]-;

Buspar(R) (Mead Johnson) ;

It is found to be useful in the treatment of anxiety and its effectiveness is fairly comparable to that of **diazepam**. It alleviates anxiety without producing sedation or functional impairment. It neither promotes abuse nor physical dependence.

2.7.1. Mechanism of Action

The mechanism of action of **buspirone hydrochloride** will be discussed as under :

2.7.1.1. Buspirone Hydrochloride

The exact mechanism of its anxiolytic effect has not yet been established ; but however, seems to be altogether different in comparison to the **barbiturates** and the **benzodiazepines.** Most probably the '**drug**' essentially involves *multiple transmitter systems,* specifically those of the first-pass metabolism.

Buspirone attains peak plasma concentrations ranging between 1-6 mg mL^{-1}, usually take place within a span of 40-90 minutes. The '**drug**' gets bound to plasma protein to nearly 95% ; and excretion through urine varies between 29-63%, while through faeces between 18-38%. The elimination half-life of the unchanged drug is approximately between 2-3 hours.

Probable Questions for B. Pharm. Examinations

1. What are **'antipsychotics'** ? Classify them by giving examples of **one** potent compound from each category.
2. (*a*) Name the **two** major alkaloids isolated from the roots of *Rauwolfia serpentina* ued as **'antipsychotics'.**

   (*b*) Give their structure, chemical name and uses.

   (*c*) Discuss the synthesis of 3-diethylamino propyl ester of 3,4,5-trimethoxy benzoic acid given by Miller and Weinberg.

   (*d*) What is the relative potency of compound in (*c*) and that of Reserpine ?
3. Discuss the synthesis of the following **diphenylmethane analogues** as 'antipsychotics' :

   (*a*) Benactyzine

   (*b*) Captodiame
4. How would you synthesize **Perphenazine** and **Thioridazine** belonging to the phenothiazine group of **'antipsychotics'** ?

5. Describe **dibenzazepines** as potent 'antipsychotics'. Give the structure, chemical name and uses of **two** such drugs.
6. (*a*) Give the structure, chemical name of the following :
   (*i*) Haloperidol
   (*ii*) Droperidol.
   (*b*) Discuss the synthesis of any **one** drug.
7. Elaborate the 'mode of action' of the following **'antipsychotics'** :
   (*a*) Reserpine
   (*b*) Chlorpromazine and Perphenazine.
   (*c*) Loxapine
   (*d*) Haloperidol
   (*e*) Buspirone.
8. Give a comprehensive account of **'antipsychotics'.** Support your answer with the most potent drugs by providing structures, chemical names and uses adequately.

RECOMMENDED READINGS

1. Gennaro AR : **Remington the Science and Practice of Pharmacy,** Lippincott Williams & Wilkins, New York, 21st edn., Vol. II, 2005.
2. Griffith MC (Ed.) **USAN and the USP Dictionary of Drug Names,** United States Pharmaceutical Convention Inc., Rockville (1985).
3. **Index Nominum**, Swiss Pharmaceutical Society, Zurich (1982).
4. Jenner P. and Marden CD, In **Drugs in Central Nervous System Disorders,** DC Horwell, ed., New York, (1985).
5. King FD : **Medicinal Chemistry-Principles and Practice,** The Royal Society of Chemistry, London, 1994.
6. Lednicer D. and Mitscher LA **The Organic Chemistry of Drug Synthesis**, John Wiley and Sons New York, (1995).
7. **Martindale The Extra Pharmacopoeia**, 31st Edn., London, The Pharmaceutical, Press (1996).
8. Oldendorf WH and Dewburst WG **Principles of Psychopharmacology**, 2nd Ed., WG Clark and J. Del Guidice (Eds.), **Academic Press** New York (1978).
9. Roberts SM and Price BJ (eds.) : **Medicinal Chemistry-The Role of Organic Chemistry in Drug Research**, Academic Press, New York, 1985.
10. Strange PG : **Antipsychotic Drugs : Importance of Dopamine Receptors for Mechanisms of Therapeutic Actions and Side Effects,** *Pharmacol. Rev.,* **53** : 119, 2001.
11. Weinberger DR : **Anxiety at the Frontier of Molecular Medicine,** *N. Engl. J. Med.,* **344 :** 1247, 2001.
12. Wermuth CG : **The Practice of Medicinal Chemisty**, Academic Press, New York, 1996.